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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/801,852	03/08/2001	Shu-Jen David Chiang	ON0163NP	6300

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EXAMINER	
SLOBODYANSKY, ELIZABETH	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 06/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/801,852	CHIANG	
	Examiner	Art Unit	
	Elizabeth Slobodyansky, PhD	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6 and 8-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6 and 8-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 21, 2004 has been entered.

The AF amendment filed November 19, 2003 canceling claims 12 and 13 has been entered.

Claims 1, 3-6 and 8-11 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-6 and 8-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 3-6 and 8-10 are drawn to a method of use of a strain of *Acremonium chrysogenum* transformed with a nucleic acid encoding a *Rhodosporidium* cephalosporin esterase. Therefore, these claims recite a genus of nucleic acids encoding a *Rhodosporidium* cephalosporin esterase. This genus encompasses nucleic acids encoding any cephalosporin, including cephalosporin C, esterase from any species and strains of *Rhodosporidium.* Furthermore, said genus encompasses nucleic acids encoding esterases that hydrolyze the acetyl bond on the 10-position of a cephalosporin as well as other(s) position(s).

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, "requires a precise definition, such as be structure, formula [or] chemical name," of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, the genus of nucleic acids encoding a *Rhodosporidium* cephalosporin C esterase is represented by a genomic nucleic acid isolated from a single strain of *Rhodosporidium toruloides* (ATCC 10657) having the nucleotide sequence of SEQ ID NO:1 and corresponding cDNA having the sequence of SEQ ID NO:3. SEQ ID NOs: 1 or 3 encode cephalosporin C esterase of SEQ ID NO:2 that hydrolyzes the acetyl bond on the 10-position of cephalosporin C (Official name Cephalosporin-C deacetylase). No other nucleic acid sequences encoding a *Rhodosporidium* cephalosporin esterase are disclosed in the specification. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of encoding a *Rhodosporidium* cephalosporin esterase.

Given this lack of description of representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention, the genus of nucleic acids encoding a *Rhodosporidium* cephalosporin C esterase.

Claims 1, 3- 6 and 8-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of use of a strain of *Acremonium chrysogenum* transformed with a nucleic acid encoding a *Rhodosporidium* cephalosporin C esterase of SEQ ID NO:2, including SEQ ID NOs:1 and 3, does not reasonably provide enablement for a method of use of a strain of *Acremonium*

chrysogenum transformed with a nucleic acid encoding a *Rhodosporidium* cephalosporin C esterase having an unknown homology to SEQ ID NOs: 1 or 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, how to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The specification does not support the broad scope of the claims which encompass nucleic acids having an unknown homology to SEQ ID NOs:1 or 3 and encoding any *Rhodosporidium* cephalosporin C esterase having an unknown homology to SEQ ID NO: 2.

The specification does not teach nucleic acids encoding any *Rhodosporidium* cephalosporin C esterase other than the esterase having the amino acid sequence of SEQ ID NO: 2 encoded by SEQ ID NOs:1 or 3. While recombinant hybridization techniques are known, only highly homologous sequences can be identified using a given nucleic acid sequence. The state of the art provides no reasonable expectation of

success in obtaining nucleic acid encoding DHAK having an unknown homology to SEQ ID NO: 1 and the result of such screening is unpredictable.

Without sufficient guidance, beyond that provided, determination of nucleic acids encoding a *Rhodosporidium* cephalosporin C esterase having an unknown homology to SEQ ID NO:2, said nucleic acid having an unknown homology to SEQ ID NOs:1 or 3 is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> > (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-6 and 9-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Politino et al. (A).

Politino et al. (A), (WO 98/12345, form PTO-1449 filed January 14, 2002, reference AM) teach a DNA encoding cephalosporin C esterase from *Rhodosporidium toruloides* that is 100% identical to SEQ ID NO:3 of the instant invention and differs by one nucleotide from SEQ ID NO:1. They teach the method for producing said cephalosporin C esterase by culturing cells of *Cephalosporin acremonium* transformed

with a DNA encoding a cephalosporin esterase from *Rhodosporidium toruloides* (page 9, claims 26-28). The cells must be cultured at conditions that are standard for culturing *Cephalosporin acremonium*. These conditions would include temperature between about 22^{0}C to about 29^{0}C and the pH is about 5.5 to about 7.5. They further teach that *Cephalosporin acremonium* (*Acremonium chrysogenum*) is producing cephalosporin C and contains nucleic acid encoding enzymes for cephalosporin C biosynthesis. They teach that when a cephalosporin C esterase from *Rhodosporidium toruloides* is added, desacetylcephalosporin C is produced (Example 2). They teach that cephalosporin C is completely hydrolyzed by the esterase within 30 min at 30° C, pH 6.5, with no side products observed by HPLC (page 16, lines 14, 25-26). The conditions of "30° C" that is "about 29° C" and "pH 6.5" that is in the range of "about 5.5 to about 7.5" meet the limitations for the experimental parameters recited in claim 1.

Therefore, they teach a method for producing of desacetylcephalosporin C by culturing cells of *Cephalosporin acremonium* (*Acremonium chrysogenum*) transformed with a DNA encoding a *Rhodosporidium* esterase.

The teachings of Politino et al. further meet the limitations of the chemical breakdown of cephalosporin C of less than 40%, 30%, 20%, 10% or 5% as required by claims 1 and 3-6 because no side products were observed by HPLC (page 16, Example, 2.1).

A person shall be entitled to a patent unless -

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application

> by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 3-6 and 9-11 are rejected under 35 U.S.C. 102(e) as being anticipated by Politino et al.(B).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Politino et al. (B), (US Patent 5,869,309, form PTO-1449 filed June 14, 2001, reference AG) is US counterpart of WO 98/12345, *supra*.

Politino et al. (B) teach a DNA encoding cephalosporin C esterase from *Rhodosporidium toruloides* that is 100% identical to SEQ ID NOs: 1 or 3 of the instant

invention. They teach the method for producing said a cephalosporin C esterase by culturing cells of *Cephalosporin acremonium* transformed with a DNA encoding a cephalosporin esterase from *Rhodosporidium toruloides* (claims 17-24). The cells must be cultured at conditions that are standard for culturing *Cephalosporin acremonium*. These conditions would include temperature between about 22^0C to about 29^0C and the pH is about 5.5 to about 7.5. They further teach that *Cephalosporin acremonium* (*Acremonium chrysogenum*) is producing cephalosporin C and contains nucleic acid encoding enzymes for cephalosporin C biosynthesis. They teach that when a cephalosporin C esterase from *Rhodosporidium toruloides* is added, desacetylcephalosporin C is produced (Example 2). They teach that cephalosporin C is completely hydrolyzed by the esterase within 30 min at 30° C, pH 6.5, with no side products observed by HPLC (column 9, line 60, through column 10, line 14). The conditions of "30° C" that is "about 29° C" and "pH 6.5" that is in the range of "about 5.5 to about 7.5" meet the limitations for the experimental parameters recited in claim 1.

Therefore, they teach a method for producing of desacetylcephalosporin C by culturing cells of *Cephalosporin acremonium* (*Acremonium chrysogenum*) transformed with a DNA encoding a *Rhodosporidium* esterase.

The teachings of Politino et al. further meet the limitations of the chemical breakdown of cephalosporin C of less than 40%, 30%, 20%, 10% or 5% as required by claims 1 and 3-6 because no side products were observed by HPLC (column 9, line 60, through column 10, line 14).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Politino et al. (A) or (B) in view of Smith et al.

The teachings of Politino et al. (A) and (B) are outlined above.

Smith et al. (US Patent 4,533,632, form PTO-1449 filed June 14, 2001, reference AC) teach a process for the preparation of desacetylcephalosporin C by fermenting *Acremonium chrysogenum* in the presence of esterase from *Rhodosporidium toruloides* (claims 1-7). The process of fermentation is carried out at 15°-45° C and pH 4-9.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use *Acremonium chrysogenum* transformed with a DNA encoding *Rhodosporidium toruloides* esterase in the production of desacetylcephalosporin C. This would allow to increase and standardize the production of the esterase used in the method taught by Smith et al. Such host cells are taught by Politino et al. (A, B). It would have been further obvious to find and use optimal conditions for producing of desacetylcephalosporin C and fermenting *Acremonium chrysogenum* within the range of standard conditions taught by Smith et al.

Response to Arguments

Applicant's arguments filed April 21, 2004 have been fully considered but they are not persuasive.

With regard to the 102 (b, e) rejections, Applicants argue "Specifically, in Example 2, the esterase enzyme is added to a reaction mixture containing cephalosporin (emphasis added). A by-product of that reaction was desacetyl cephalosporin C, evidencing the efficacy of the recombinantly produced enzyme. This is not relevant, however, to a discussion of the present invention which involves a recombinant fungal organism capable of directly fermenting desacetylcephalosporin C. The Examiner has not provided a reference showing a process for the direct production of desacetylcephalosporin C which comprises culturing a strain of Acremonium chrysogenum that contains (1) nucleic acid encoding enzymes for cephalosporin C biosynthesis and (2) a recombinant nucleic acid encoding *Rhodosporidium* cephalosporin esterase, under the stated conditions" (Remarks, page 4, 3rd paragraph). This is not agreed with because Politino et al. (A, B) teach a method for producing a polypeptide of SEQ ID NO:2 having cephalosporin esterase activity (*Rhodosporidium* cephalosporin esterase) comprising a single step of culturing the host cell (*Cephalosporin acremonium*) under conditions resulting in expression of the polypeptide (claims 26-28). Thus, said method comprises the same step of culturing of a strain of *Acremonium chrysogenum* (a.k.a. *Cephalosporin acremonium*) transformed with a nucleic acid encoding the *Rhodosporidium* cephalosporin esterase that is identical to the nucleic acid of the instant invention. The intended use, i.e. for the production of the

esterase or for the production of desacetylcephalosporin C, does not impart the patentability to the method that consists of the same step of culturing a single recombinant organism which produces both cephalosporin C and cephalosporin esterase as claimed in the instant invention and the prior art. Said process is a process for the production of the esterase and at the same time the process for the direct production of desacetylcephalosporin C using a single recombinant organism which produces both cephalosporin C and cephalosporin esterase. Claim 1 additionally recites temperature and pH under which the recombinant *Acremonium chrysogenum* is cultured. Those are the regular conditions used for culturing recombinant cells and *Acremonium chrysogenum* cells, i.e. room temperature and a slightly acid to neutral pH. Politino et al. teach that these conditions are optimal for the esterase activity.

Applicants further argue that "The Examiner points specifically to Claims 26-28 in Politino (A). However, those claims do not set forth the process of the present invention. Applicants point out that cloning of the gene coding for the enzyme is required for heterologous expression of an active enzyme, but it does not necessarily follow that the enzyme will be readily expressed in an active form. In fact, efforts to express this enzyme in an *E. coli* host did not result in an active protein, as describe at pages 37-38 of the present specification. As discovered in the present invention, active expression of the enzyme requires a suitable glycosylation pattern, intron splicing and removal of the N-terminal leader sequence. Therefore, the expression of the esterase enzyme is *A. Chrysogenum* under conditions which allow sufficient expression for the esterase enzyme for the conversion of cephalosporin C to desacetylcephalosporin, such that the

conditions of the present claims are 'satisfied, are not set forth in Politino (A)" (page 5, 1st paragraph, emphasis in original). This is not persuasive because as explained in the preceding paragraph, those claims do set forth the process of the present invention. Said process uses a transformed *A. chrysogenum*, the exactly same cell that is proven to produce an active esterase in the present invention. Whether *E. coli* can be used for the expression of an active esterase is irrelevant because the claimed process does not use a transformed *E. coli.*

Applicants further argue that "The Examiner is respectfully requested to point out where each and every element of the present claims (as required by Section 102) are set forth in Politino (A), present Claim 1 having the following elements: (1) a process for the direct production of desacetylcephalosporin C which includes; (2) culturing a strain of *Acremonium chrysogenum* containing nucleic acid encoding enzymes for (a) cephalosporin C biosynthesis and (b) a recombinant nucleic acid encoding *Rhodosporidium* cephalosporin esterase (3) under conditions wherein the temperature is about 22^0C to about 29^0C and the pH is about 5.5 to about 7.5 (4) resulting in the synthesis of cephalosporin C and expression of cephalosporin esterase (5) wherein the cephalosporin C so produced is converted to desacetylcephalosporin C and (6) the chemical breakdown of cephalosporin C to 2-(D-4-amino-4-carboxybutyl)-thiazole-4-carboxylic acid is less than 40%" (page 5, 2nd paragraph).

As explained above, the process comprising a single step of culturing a strain of *Acremonium chrysogenum* containing nucleic acid encoding enzymes for (a) cephalosporin C biosynthesis and (b) a recombinant nucleic acid encoding

Rhodosporidium cephalosporin esterase is disclosed in Politino et al. references. The references teach that *Acremonium chrysogenum* naturally contains nucleic acid encoding enzymes for cephalosporin C biosynthesis. Thus, an *Acremonium chrysogenum* transformed with a DNA encoding a *Rhodosporidium* cephalosporin esterase directly produces both cephalosporin C esterase and desacetylcephalosporin C. The conditions wherein the temperature is about 22^{0}C to about 29^{0}C and the pH is about 5.5 to about 7.5 are standard conditions for culturing of *Acremonium chrysogenum.* The references teach that the chemical breakdown of cephalosporin C to 2-(D-4-amino-4-carboxybutyl)-thiazole-4-carboxylic acid is less than 40%", *supra.*

With regard to the 103(a) rejection, Applicant's argue that The Examiner has maintained the rejection of Claim 8 under 35 U.S.C. §103(a) as being unpatentable over Politino (A) or (B) in view of U.S. Patent No. 4,533,632 ("Smith"). The Examiner alleges that Smith teaches a process for the preparation of desacetylcephalosporin C by fermenting *Acremonium chrysogenum* in the presence of esterase from *Rhodosporidium toruloides*. The process of fermentation is carried out at 15^0-45^0 C and pH 4-9. The Examiner alleges that it would have been obvious at the time of the present invention to use *Acremonium chrysogenum* transformed with a DNA encoding *Rhodosporidium toruloides* esterase in the production of desacetylcephalosporin C.

The Examiner has only made conclusory statements without providing the requisite motivation necessary for a proper rejection under Section 103. The Examiner states that the motivation is provided at pages 6-7 of the Final Office Action, but Applicants again submit that these are merely conclusory statements. The Examiner

does not point to specific instances within the references where the motivation is provided. In any event, Applicants submit that the point is moot as the deficiencies of Politino (A) and (B) noted above cannot, of course, be remedied by the teachings of Smith. The examiner disagrees. The Smith reference is provided to evidence the conditions for culturing of *Acremonium chrysogenum*. One of ordinary skill in the art is motivated to use the known standard conditions for culturing of any given cell, including an *Acremonium chrysogenum* cell.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky, PhD whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, PhD can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner
Art Unit 1652

June 25, 2004